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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/331,980	CHAGNAUD ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-27* is/are pending in the application.

4a) Of the above claim(s) *7-10,12,13 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 11, 14 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5 and 7-27 are pending.

2. It is noted that claim 6 has been canceled by preliminary amendment filed 6/30/99. Claim 6 is NOT withdrawn as stated in the listing of claims in amendment filed 2/27/04. A claim canceled by amendment (deleted in its entirety) may be reinstated only by a subsequent amendment presenting the claim as a new claim with a new claim number. See 37 CFR 1.121(c).

3. Claims 7-10, 12-13 and 15-20 stand withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 1-5, 11, 14 and 21-27 drawn to a purified antibody that binds to specifically to a nitrosylated protein are being acted upon in this Office Action.

5. The substituted specification filed 10/21/02 has been entered.

6. The drawings, filed 3/4/02, stand not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review mailed 5/20/02. Appropriate action is required. It is noted that Applicants will provide formal figures upon receipt of a Notice of Allowance.

7. The following new grounds of rejections are necessitated by the amendment filed 2/27/04.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 11, 14, and 22-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a purified antibody that binds specifically to NO-Cys-glutaraldehyde conjugated to a carrier protein such as BSA for detection assay, **does not** reasonably provide enablement for *any* purified antibody such as any polyclonal or monoclonal antibody that recognizes and binds specifically to all "nitrosylated protein", *any* purified antibody such as any polyclonal or any monoclonal antibody that neutralizes the deleterious effects of "inadequate production of nitric oxide or its conjugates" in all subject, *any* purified antibody such as any polyclonal or any monoclonal antibody that recognizes and binds specifically to all nitrosylated epitope such that the antibody masks the nitrosylated epitope of all protein (claim 22), the purified antibody that recognizes and binds specifically to all nitrosylated epitope such that the antibody masks the nitrosylated epitope of all protein further comprises a coupling agent such as glutaraldehyde or succinic anhydride, *any* pharmaceutical composition or kit comprising the antibody mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two polyclonal antibodies that bind specifically to nitrosylated cysteine-glutaraldehyde conjugated to BSA (NO-Tyr-BSA) or NO-Cys-BSA) for in vitro and in vivo detection assays (page 33). The anti-No-cys-G-BSA and anti-No-Tyr-BSA neutralizes the effect of NO in Lewis rat injected with encephalitogenic Peptide from the Guinea Pig (EAE model) or the adjuvant induced arthritis. The specification further discloses monoclonal antibody that binds specifically to NO-Cys-G protein conjugate for in vitro detection of certain NO binding sites such as cysteine in parasites (page 38).

The specification does not teach how to make any antibody that binds to any nitrosylated protein, much less using any undisclosed antibody as a pharmaceutical composition for

neutralizing the deleterious effects of "*inadequate* production of nitric oxide or its conjugates in any subject". There is insufficient guidance as to the binding specificity of any undisclosed antibody such as monoclonal or polyclonal antibody that binds to all "nitrosylated protein", much less the immunogen used for making antibody that would bind to all nitrosylated protein without the amino acid sequence. A nitrosylated protein without the amino acid sequence has no structure, much less function. Without the immunogen, it would take undue experimentation even for one skilled in the art to arrive at the claimed antibody. Given the indefinite number of undisclosed nitrosylated protein, it is unpredictable which undisclosed immunogen would produce antibody such as polyclonal or monoclonal antibody binds to all nitrosylated protein. Further there is insufficient in vivo working example demonstrating that all undisclosed antibody such as monoclonal and polyclonal antibody what would neutralizes the "*inadequate* production" of nitric oxide or its conjugates in a subject. With regard to antibody binding to a nitrosylated epitope, it is not clear which amino acid residue on which protein that the claimed antibody binds.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of nitrosylated protein and without the specific amino acid sequence to which the undisclosed antibody binds, it is unpredictable which undisclosed antibody generated from any nitrosylated protein would binds specifically to NO-Cys-glutaraldehyde conjugated to BSA, in turn, would be useful for neutralizing the deleterious effects of excessive production of nitric oxide such as autoimmune arthritis, EAE in a subject or neutralizing the deleterious effects of "inadequate production of nitric oxide".

Even if the antibody is limited to the specific antibodies mentioned above, there is insufficient in vivo working example demonstrating that the antibodies mentioned above are effective for neutralizing the deleterious effects of "inadequate production of nitric oxide" or its conjugates in any subject. It is known that excessive nitric oxide production by activated macrophage may be one of the causes for the deleterious effects in inflammatory rheumatoid arthritis. However, it is not known that "inadequate production of nitric oxide" and its conjugate

is the cause of any inflammatory disease. The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering any antibodies that neutralizes the deleterious effects of *inadequate production of nitric oxide or its conjugates*. Therefore, it is not clear that the skilled artisan could predict the efficacy of the pharmaceutical composition comprising any antibodies with questionable binding specificity. Since the binding specificity of any antibody is not enabled, it follows that any pharmaceutical composition and kit comprising said undisclosed antibody is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/27/04 have been fully considered but are not found persuasive.

Applicants' position is that the instant application does not just disclose detection systems, but discloses two different experimental diseases in vivo: autoimmune encephalitis and inflammatory arthritis (page 54, line 25 to page 66, line 10). Applicants have provided a number of example antibodies that fall within the scope of the claimed invention. One skill in the art can practice the claimed invention.

The scope of the claims encompasses any antibody that recognizes and binds to all nitrosylated protein. The specification discloses only anti-No-cys-G-BSA and anti-No-Tyr-BSA antibodies that bind to NO-Cys-BSA or NO-tyr-BSA. The anti-No-cys-G-BSA and anti-No-Tyr-BSA antibodies neutralize the effect of NO in Lewis rat injected with encephalitogenic peptide from the Guinea Pig (EAE model) or the adjuvant induced arthritis. Both models involve excessive production of nitric oxide.

There is insufficient guidance as to the binding specificity of all undisclosed antibody such as monoclonal or polyclonal antibody that binds to all "nitrosylated protein", much less the immunogen used for making such antibody. A "nitrosylated protein" without the amino acid

sequence has no structure, much less function. Without the immunogen, it would take undue experimentation even for one skilled in the art to arrive at the claimed antibody. Further, there is insufficient in vivo working example demonstrating that all undisclosed antibody such as monoclonal and polyclonal antibody would neutralizes the "inadequate production of nitric oxide or its conjugates in a subject". The specification teaches that excessive NO production is the culprit in the encephalitis and adjuvant induced arthritis models. It is not clear how the claimed antibody could neutralize the "inadequate production" of nitric oxide or its conjugates in a subject. There is insufficient guidance as to which particular disease is associated with "inadequate production" of nitric oxide or its conjugates for the claimed pharmaceutical composition. With regard to antibody binding to a nitrosylated epitope, it is not clear which amino acid residue on which protein that the claimed antibody binds.

10. Claims 1-5, 11, 14, and 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* purified antibody such as any polyclonal or monoclonal antibody that recognizes and binds specifically to all "nitrosylated protein", *any* purified antibody such as any polyclonal or any monoclonal antibody that neutralizes the deleterious effects of "inadequate production of nitric oxide or its conjugates" in all subject, *any* purified antibody such as any polyclonal or any monoclonal antibody that recognizes and binds specifically to all nitrosylated epitope such that the antibody masks the nitrosylated epitope of all protein (claim 22), the purified antibody that recognizes and binds specifically to all nitrosylated epitope such that the antibody masks the nitrosylated epitope of all protein further comprises a coupling agent such as glutaradehyde or succinic anhydride, *any* pharmaceutical composition or kit comprising the antibody mentioned above.

The specification discloses only two polyclonal antibodies that bind specifically to nitrosylated cysteine-glutaraldehyde conjugated to BSA (NO-Tyr-BSA) or NO-Cys-BSA) for in vitro and in vivo detection assays (page 33). The anti-No-cys-G-BSA and anti-No-Tyr-BSA neutralizes the effect of NO in Lewis rat injected with encephalitogenic Peptide from the Guinea Pig (EAE model) or the adjuvant induced arthritis. The specification further discloses monoclonal

antibody that binds specifically to NO-Cys-G protein conjugate for in vitro detection of certain NO binding sites such as cysteine in parasites (page 38).

With the exception of the specific antibodies that neutralize NO by immunizing with specific nitrosylated albumin, there is insufficient written description about the binding specificity of all purified antibody that bind to all nitrosylated protein or which nitrosylated epitope on which protein without the amino acid sequence. Since the binding specificity of the claimed antibody is not adequately described, it follows that the pharmaceutical composition and kit comprising the undisclosed antibody are not adequately described. Given the lack of a written description of *any* additional representative species of antibodies mentioned above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "cysteine, tyrosine or tryptophan" in claim 21 is ambiguous and indefinite because these cysteine, tyrosine and tryptophan residues are found within the albumin or BSA. It is not clear the cited cysteine, tyrosine and tryptophan residues are extra amino acid residues added to either the albumin or the BSA, or the cysteine, tyrosine and tryptophan residues that are found within the albumin or BSA. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-4, and 21-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892).

Boullerne *et al* teach a purified antibody that is isolated from a patient with MS. The reference antibody recognizes and binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin or NO-Cys-g-BSA. The reference autoantibody isolated from sera of Multiple sclerosis (MS) is polyclonal (See page 123, column 1, first paragraph, in particular). Boullerne et al further teach that the reference antibody can be purified using nitrosylated carrier protein (nitrosylated bovine serum albumin) or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA in **Materials and Methods**, pp. 118-119, in particular). Antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular). Boullerne *et al* further teach that NO production may be involved in autoimmune diseases including IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular). Claim 2 is included in this rejection because Nitrosylated protein inherently is a transporter of nitric oxide. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 2/27/04 have been fully considered but are not found persuasive.

Applicants' position is that Boullerne detect specific antibodies in MS sera capable of reacting with NO-Cys-g-BSA. Boullerne et al do not purify antibodies. Boullerne does not describe the in vivo analysis performed by the inventors in the instant application.

However, the detected specific antibody taught by Boullerne binds to a nitrosylated protein such as NO-Cys-g-BSA that comprises a cysteine, a coupling agent such as glutaldehyde (g) and BSA. The reference antibody in the serum is not in the patient with MS (See page 119, column 1, in particular). Boullerne et al further teach that the reference antibody can be purified using nitrosylated carrier protein (nitrosylated bovine serum albumin) or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA in **Materials and Methods**, pp. 118-119, in particular). Further, the specificity of the claimed antibody appears to the same as that of the prior art. Since

the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

15. Claims 1-5, 11 and 21-26 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0736770 A2 published October 9, 1996; PTO 1449).

The EP 0736770 A2 patent teaches various purified antibodies such as polyclonal and monoclonal antibodies that bind to a nitrosylated protein such as NO-Cys (acetylated) bovine albumin (See page 8, line 45, Table 1, page 3, line 35, page 4, lines 51-52, in particular). EP 0736770 A2 further teaches the nitrosylated BSA further comprises a coupling agent such as carbodiimide, or succinic anhydride (See page 6, line 14-18, in particular). The reference nitrosylated BSA is NO-Cys(acetylated)-BSA or NO-cys (non-acetylated)-BSA (See page 3, line 34-35, in particular). The EP 0736770 A2 patent teaches a pharmaceutical composition comprising the reference antibody and a pharmaceutically acceptable excipient (See page 3, lines 22-24, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 2/27/04 have been fully considered but are not found persuasive.

Applicants' position is that Applicants have filed a certified copy of the French priority document (FR 96/16027) and the statement of Scott D. Miller which states that application serial number 09/331,980 (instant application) is an accurate translation of FR 96/16207. Accordingly, the priority date of the instant application should be deemed to be December 30, 1996.

However, the EP 0736770 A2 is published October 9, 1996, which is more than one year prior to the effective filing date 12/23/1997 of the present application. The EP 0736770 A2 reference is a statutory bar under 35 U.S.C. 102(b).

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 14, 21-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0736770 A2 published October 9, 1996; PTO 892) in view of WO 96/04311 (Feb 1996, PTO 892).

The teachings of EP 0736770 A2 patent have been discussed supra.

The claimed invention in claim 14 differs from the teachings of the reference only in that a kit for in vitro detection of nitrosylated proteins in biological specimen, the kit comprising the purified antibody that recognizes and binds specifically to nitrosylated protein and reagents to produce a medium favorable for immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen.

The claimed invention in claim 27 differs from the teachings of the reference only in that a kit for in vitro detection of nitrosylated proteins in biological specimen, the kit comprising the purified antibody that recognizes and binds specifically to nitrosylated BSA (NO-Cys-(acetylated)-BSA) and reagents to produce a medium favorable for immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen.

The WO 96/04311 publication teaches a kit comprising monoclonal or polyclonal antibody to nitrotyrosine and reagents for detecting nitrotyrosine and anti-nitrotyrosine (See claims 25-26 of WO 96/04311 publication, page 5, summary of invention, page 7, line 6-20, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in a kit taught by the WO 96/04311 publication for the antibody that binds to NO-Cys (acetylated) BSA as taught by the EP 0736770 A2 patent for diagnostic assays as taught by the WO 96/04311 publication. One would have been motivated, with a reasonable expectation of success, to place the antibody taught by the EP 0736770 A2

patent in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by WO 96/04311 publication (claims 25-26 of WO 96/04311 publication, page 8, line 30in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

19. Claims 1, 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892) in view of U.S. Pat No. 6,090,382 (of record, July 2000, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

Boullerne *et al* teach nitrosylated carrier protein such as nitrosylated bovine serum albumin or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA (See Materials and Methods, pp. 118-119, in particular). Boullerne *et al* teach antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular). Boullerne *et al* further teach that NO production may be involved in autoimmune diseases such as IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular).

The claimed invention in claim 5 differs from the teachings of the reference only in that the antibody is a monoclonal antibody.

The claimed invention in claim 11 differs from the teachings of the reference only in that a pharmaceutical composition comprising (a) a purified antibody that recognizes and binds specifically to a nitrosylated protein and (b) a pharmaceutically acceptable vehicle wherein the purified antibody neutralizes the deleterious effects of excessive production of nitric oxide in a subject.

The '382 patent teaches a pharmaceutical composition comprising an antibody that binds to human TNFα and a pharmaceutical acceptable carrier or excipient such as sterile saline (See column 20 lines 57, bridging column 21, line 1-52, in particular).

Campbell *et al* teach that "[i] it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section "Basic research", in particular).

Harlow *et al* teach a method of producing monoclonal antibody (See page 139-149, in particular). Harlow *et al* further teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Campbell *et al* or Harlow *et al* with the nitrosylated protein as taught by Boullerne *et al* in a pharmaceutical composition comprising a monoclonal antibody that binds specifically to the nitrosylated protein and a pharmaceutical excipient as taught by the '382 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make monoclonal antibody because Harlow *et al* teach the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Campbell *et al* teach that "[i] it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section "Basic research", in particular). Boullerne *et al* teach antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular); NO production may be involved in autoimmune diseases including IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular). The '382 patent teaches a pharmaceutical composition comprising an antibody that binds to human TNFα and a

pharmaceutical acceptable carrier or excipient such as sterile saline (See column 20 lines 57, bridging column 21, line 1-52, in particular).

Applicants' arguments filed 2/27/04 have been fully considered but are not found persuasive.

Applicants' position is that Boullerne detect specific antibodies in MS sera capable of reacting with NO-Cys-g-BSA. Boullerne et al do not purify antibodies. Boullerne does not describe the in vivo analysis performed by the inventors in the instant application.

However, the detected specific antibody taught by Boullerne binds to a nitrosylated protein such as NO-Cys-g-BSA that comprises a cysteine, a coupling agent such as glutaldehyde (g). The reference antibody is isolated or purified from serum of patient with MS (See page 119, column 1, in particular). Boullerne et al further teach that the reference antibody can be purified using nitrosylated carrier protein (nitrosylated bovine serum albumin) or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA in **Materials and Methods**, pp. 118-119, in particular). A product is a product, irrespective of how it is made.

20. Claims 1, 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892) in view of U.S. Pat No. 6,090,382 (of record, July 2000, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149) as applied to claims 1, 5 and 11 mentioned above, and further in view of U.S. Pat No. 5,858,682 (of record, Jan 1999, PTO 892; see entire document).

The combined teachings of Boullerne *et al*, the '382 patent, Campbell *et al* and Harlow *et al* have been discussed supra.

The claimed invention in claim 14 differs from the teachings of the references only in that a kit for in vitro detection of nitrosylated proteins in biological specimen comprising a purified antibody that recognizes and binds specifically to a nitrosylated protein and reagents to produce a medium favorable for an immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen.

The '682 patent teaches a kit comprising antibody for diagnostic (See column 3, line 40; column 6, line 17; column 8, line 36, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in a kit taught by '682 with the polyclonal antibody that binds nitrosylated protein taught by as taught by Boullerne *et al or* the monoclonal antibody by binds specifically to nitrosylated protein as taught by Boullerne *et al,* and Campbell *et al* or Harlow *et al* for the detection of nitrosylated protein immune complex in any biological specimen as taught by Boullerne *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One would have been motivated, with a reasonable expectation of success, to place the antibody in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '682 (See column 8, line 36-57, in particular).

Applicants' arguments filed 2/27/04 have been fully considered but are not found persuasive.

Applicants' position is that Boullerne detect specific antibodies in MS sera capable of reacting with NO-Cys-g-BSA. Boullerne et al do not purify antibodies. Boullerne does not describe the in vivo analysis performed by the inventors in the instant application.

However, the detected specific antibody taught by Boullerne binds to a nitrosylated protein such as NO-Cys-g-BSA that comprises a cysteine, a coupling agent such as glutaldehyde (g). The reference antibody is isolated or purified from serum of patient with MS (See page 119, column 1, in particular). Boullerne et al further teach that the reference antibody can be purified using nitrosylated carrier protein (nitrosylated bovine serum albumin) or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA in **Materials and Methods**, pp. 118-119, in particular). A product is a product, irrespective of how it is made.

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

24. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 14, 2004

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